Available online at www.sciencedirect.com
ScienceDirect
Domestic Animal Endocrinology 36 (2009) 111–126
DOMESTIC ANIMAL ENDOCRINOLOGY
www.domesticanimalendo.com

Invited review

Extrinsic regulation of domestic animal-derived myogenic satellite cells II

R.P. Rhoads[a,1], M.E. Fernyhough[b,1], X. Liu[a,1], D.C. McFarland[c,1], S.G. Velleman[d,1], G.J. Hausman[e,1], M.V. Dodson[f,*,1]

[a] *Department of Animal Sciences, University of Arizona, Tucson, AZ 85719, United States*
[b] *The Hartz Mountain Corporation, Secaucus, NJ 07094, United States*
[c] *Department of Animal and Range Sciences, South Dakota State University, Brookings, SD 57007, United States*
[d] *The Ohio State University/OARDC, Wooster, OH 44691, United States*
[e] *USDA-ARS, Richard B. Russell Agricultural Research Station, Athens, GA 30604, United States*
[f] *Department of Animal Sciences, Washington State University, Pullman, WA 99164, United States*

Received 17 November 2008; received in revised form 18 December 2008; accepted 19 December 2008

Abstract

The existence of myogenic satellite cells was reported some 47 years ago, and, since that time, satellite cell research has flourished. So much new information is generated (daily) on these cells that it can be difficult for individuals to keep abreast of important issues related to their activation and proliferation, the modulation of the activity of other cell types, the differentiation of the cells to facilitate normal skeletal muscle growth and development, or to the repair of damaged myofibers. The intent of this review is to summarize new information about the extrinsic regulation of myogenic satellite cells and to provide specific mechanisms involved in altering satellite cell physiology. Where possible, examples from agriculturally important animals are used for illustrative purposes. Published by Elsevier Inc.

Keywords: Satellite cells; Extrinsic regulation; Extracellular matrix; Steroids; Growth factors

Contents

1. Introduction 112
2. Satellite cell *in vitro* versus *in vivo* 112
3. Satellite cells and their microenvironment: proteoglycan regulation of satellite cell proliferation and differentiation 112
4. Extrinsic regulation of satellite cells by growth factors/inhibitors 114
   4.1. Insulin-like growth factors 114
   4.2. Myostatin 115
   4.3. Fibroblast growth factor 115
   4.4. Hepatocyte growth factor 116
5. Steroid hormones 117

* Corresponding author.
E-mail address: dodson@wsu.edu (M.V. Dodson).
[1] These authors contributed equally to this work.

0739-7240/$ – see front matter. Published by Elsevier Inc.
doi:10.1016/j.domaniend.2008.12.005

6. Muscle-specific transcription factors (MRF) and expression of Pax proteins 118
7. Nutrition and satellite cells 119
8. Satellite cells and other cell phenotypes 119
9. Nerves and satellite cells 121
10. Implications 121
References 121

1. Introduction

Myogenic satellite cells remain mysterious [1]. Residing alone in postnatal skeletal muscle [2,3], it may rest in an inactive state for some duration [4]. When signaled to activate [5–7], a satellite cell may leave its dormant state and become a myogenic progenitor cell-producing dynamo, with resultant daughter myocytes functioning to add myonuclei to growing skeletal muscle myofibers, or forming new myofibers in the place of damaged muscle cells [2–4,8–10]. Other functions of the satellite cell have been proposed [3] and, considering that more than one type of satellite cell may exist in skeletal muscle [11] or that some satellite cells may actually be derived from other tissues/cells [1,8,10], it is important to periodically assess the state of the rapidly evolving field of satellite cell biology as it pertains to domestic animals. As such, the focus of this review is to update our previous review [12] and provide new information about the extrinsic regulation of domestic animal-derived myogenic satellite cells.

2. Satellite cell *in vitro* versus *in vivo*

Numerous papers (primarily using rodent-derived satellite cells) have been published since 1996 involving the animal (or animal treatment) as a major experimental unit and satellite cell activity as a measure of *in vivo* action. The implantation of animals with anabolic agents and the subsequent effect on satellite cells was a common protocol [13,14], as was comparing high growth to slow growth animals. In these studies satellite cell number and activity *in vitro* was the measure of *in vivo* physiology. Other studies were published that focused on specific mechanisms involved in satellite cell proliferation and/or differentiation, as modulated by regulatory agents (numerous references within this review).

A little over 10 years ago, a main goal of satellite cell research was to develop species-specific satellite cell cultures [12,15,16]. Another goal was to generate cell cultures (regardless of species used for muscle tissue procurement) that possessed few contaminating cells such as fibroblasts, which co-isolated with satellite cells during cell isolation regimens. Because these contaminating cells potentially could overrun cultures and provide biased measures of cell activity *in vitro*, diligence was needed to insure that culture systems were controlled and interpretable. Similar to research conducted in the late 1990s, present day satellite cell researchers also worry about cell contamination. However, the cell type that is of concern (today) is a population of undefined cells, which are reminiscent of mesodermal stem cells and are not satellite cells. This new population of cells shows promise for use in numerous biotechnologies, including generalized tissue engineering, cellular cardiomyoplasty, and myoblast transfer therapy. Separating the influence of postnatal myogenic satellite cells and the new stem cell population will consume time and energy for some time to come.

Primary, clonal, and isolated myofiber cultures have all been used to address aspects of satellite cell physiology/regulation [17–19]. There are both critics and proponents of the use of these *in vitro* systems. In all circumstances, the extrapolation of *in vitro* data back to the whole animal is limited. Alternatively, the use of *in vitro* systems for determining the developmental biology of satellite cells has resulted in considerable, and useful, data. Most of our information presented in our previous review in 1996 dealt with external regulation on myogenic satellite cell activity [12]. The main focus of this review is to inform the reader about new knowledge that has surfaced since our last review.

3. Satellite cells and their microenvironment: proteoglycan regulation of satellite cell proliferation and differentiation

The activation, proliferation, and differentiation of muscle cells including the satellite cells are largely regulated in part by their interaction with the extracellular matrix (ECM) environment surrounding the muscle cells. The ECM consists of fibrous proteins (e.g., collagens) embedded in a mixture of nonfibrous macromolecules and proteoglycans. Proteoglycans, by definition, contain a core protein with at least one covalently attached glycosaminoglycan (GAG) carbohydrate

chain [20]. Glycosaminoglycans attached to the core protein include heparan sulfate (HS), chondroitin sulfate, dermatan sulfate, and keratan sulfate. Proteoglycan function is now known to depend on the core protein structure, the attached GAG chains, and the conformation of the molecule—not just the attached GAG chains as was traditionally thought [21].

The ECM modulates the activation of signal transduction pathways critical to tissue differentiation. The dynamic nature of the ECM is important to this role in that the composition of the matrix changes as the tissue ages and is cell type specific. This remodeling of the ECM has profound effects on the function of the ECM as well as cellular responses to ECM-mediated signal transduction pathways. The proteoglycan component of the ECM participates in a variety of biological processes essential for muscle growth and development including cell migration, cell adhesion, and growth factor regulation [22]. Osses and Brandan showed that proteoglycan synthesis is required for skeletal muscle differentiation [23].

Heparan sulfate proteoglycans are located at both the cell surface and in the ECM. Members of the cell surface HS proteoglycans include the transmembrane syndecans, betaglycan, CD 44, and the glycosylphosphoinositol (GPI)-linked glypicans. The syndecan and glypican families are involved in the formation of receptor-signaling complexes, especially with fibroblast growth factor 2 (FGF2). Fibroblast growth factor 2 is a potent effector of muscle cell proliferation and a strong inhibitor of differentiation. The molecular mechanisms regulating FGF2 signal transduction can have a significant impact on muscle development and growth.

The syndecans are type I transmembrane HS proteoglycans that may also have attached chondroitin sulfate chains. There are four members of the syndecan family, 1–4; all have been found in skeletal muscle. The syndecans all have an N-terminal signal peptide, an extracellular domain that contains attachment sites for the glycosaminoglycans, a transmembrane domain, and a cytoplasmic domain. The transmembrane and cytoplasmic domains are conserved across species and within the syndecans [24].

The HS chains attached to the syndecan core protein extracellular domain bind to FGF2. The binding of FGF2 to the HS chains leads to a dimerization of FGF2 permitting high-affinity binding to its tyrosine kinase receptor. This is then followed by the activation of intracellular tyrosine kinase signaling pathways, which include the mitogen-activated protein (MAP) kinase pathway, protein kinase C α (PKCα) pathway, and phosphoinositide-3 (PI3) pathway [25]. Modifications in the structure of the HS chains or degradation of these GAG chains will likely lead to changes in growth factor signal transduction.

In addition to the HS chains regulating the biological activity of the syndecans, the syndecan core protein plays a role in syndecan function. Cell adhesion, migration, and cytoskeletal signaling are some of the processes dependent on the core protein. Although the syndecans share structural similarities, each of the syndecans has unique functional attributes and tissue expression patterns. For example, the cytoplasmic domain of syndecan-4 has been shown to play an integral role in focal adhesion formation [26,27] and the activation of the PKC α pathway [25]. With the activation of the PKC α pathway, PKC α is translocated to the cell membrane and stimulates the expression of focal adhesion kinase [27] and the anti-apoptotic gene Bcl-2 [28].

The glypicans, unlike the syndecans, are not transmembrane HS proteoglycans, but are attached to the cell surface through a GPI lipid anchor. There have been six vertebrate glypicans identified: glypican-1 through -6 whose structure is conserved among the different forms. The glypicans contain an N-terminus signal sequence followed by a globular domain containing multiple cysteine residues, a GAG attachment domain, and a C-terminus that results in the formation of the GPI anchor to the cell surface. To date, only HS GAG chains have been reported to be attached to the glypican core protein. Similar to the syndecans, the glypicans bind ligands to their GAG chains, including FGF2 that permit a high-affinity interaction with their receptors, activating cell signaling pathways. Unlike the syndecans, which have cytoplasmic domains to function in the activation of signaling pathways, glypican-mediated activation of signaling pathways must be indirect and involve other transmembrane molecules since glypican does not have a transmembrane domain.

Another fashion in which glypican may regulate the activity of attached ligands is through its shedding from the cell membrane into the ECM, which has been hypothesized to be an important function of glypican-1 during skeletal muscle development [29]. Glypican-1 expression increases during the differentiation of skeletal muscle cells including satellite cells [30–32]. Brandan et al. [32] demonstrated that the increase in glypican-1 expression during differentiation coincides with increased glypican-1 shedding into the ECM. Since FGF2 is a potent inhibitor of differentiation, it is thought that the shedding of glypican-1 removes FGF2 from the cell surface and inhibits binding to its receptor [32]. The overexpression of glypican-1 in turkey

satellite cells increased the size of the myotubes formed *in vitro* after differentiation was induced, which may be the result of glypican-1 sequestering FGF2 [24]. Further research is needed to address the role of glypican-1 shedding in the regulation of FGF2 signal transduction.

Decorin is a dermatan sulfate proteoglycan belonging to the small leucine-rich proteoglycan family [33,34]. It is widely expressed in various tissues including skeletal muscle [35]. The decorin core protein has 10–14 leucine–rich repeats at its central domain and a negatively charged dermatan/chondroitin sulfate chain. Decorin is a key proteoglycan in regulating both extracellular matrix properties and cellular growth.

Decorin functions as a key modulator in the assembly and maintenance of the ECM in tissues by binding to fibrillar collagens by its core protein [36]. Targeted inactivation of the decorin gene results in abnormal collagen fibril morphology and fragile skin [37]. Rühland et al. demonstrated that the decorin chondroitin/dermatan sulfate GAG chain influences early collagen fibrillogenesis by reducing the fibrillar diameter of collagen [38]. Thus, decorin functions in the maturation of collagen fibrils into larger fibrils and fiber networks. In skeletal muscle function, this is an important consideration in regulating the elasticity and tensile strength of muscle tissue.

Muscle cell growth properties are also regulated by decorin-mediated modulation of the activity of several growth factors. For example, transforming growth factor-β1 (TGF-β1) is a strong inhibitor of both myoblast proliferation and differentiation [39]. Decorin interacts with TGF-β1 and modulates TGF-β-dependent cell growth stimulation or inhibition [40]. In both the mouse dystrophic model [41] and human Duchenne muscular dystrophy [42], the expression of both decorin and TGF-β1 is up-regulated. *In vitro*, decorin-null myoblasts not expressing decorin show a decrease in their responsiveness to TGF-β1 [43]. This indicates that the expression of decorin may mediate the ability of myoblasts to respond to TGF-β1 signaling, thus regulating cell proliferation and differentiation. Decorin's regulation of TGF-β1 signaling in non-differentiated myoblasts is through the lipoprotein-receptor related protein [44]. Myostatin, a TGF-β1 family member, is a strong inhibitor of muscle growth (discussed below). Myostatin has been shown to play a significant role in modulating muscle mass with the suppression of myostatin resulting in the double muscling phenotype seen in Piedmontese and Belgian Blue cattle [45]. Decorin regulates myostatin function by directly interacting with myostatin to suppress myostatin's inhibitory effects on muscle cell proliferation and differentiation [46]. Furthermore, the overexpression of decorin by gene transfer decreases myostatin expression at both the mRNA and protein levels and promotes muscle cell differentiation and regeneration [47].

Current research has directly demonstrated that proteoglycans are associated with the transmission of growth factor signaling and that the proliferation and differentiation of satellite cells are greatly impacted by the presence of proteoglycans. However, much still needs to be learned about the growth factor regulation of proteoglycans. For example, many of the proteoglycans are structurally similar but their functions and expression are completely unique. Elucidating the mechanisms responsible for controlling the specificity of each of these proteoglycans is a critical area for future research.

4. Extrinsic regulation of satellite cells by growth factors/inhibitors

The contribution of the satellite cell in maintaining, repairing, and regulating muscle mass is dependent upon the ability of the satellite cell to respond to a variety of extrinsic signals [6,18,19,48]. In the sections that follow, this review will highlight the extrinsic factors, such as growth factors, generating a high level of research interest—although it should be noted that investigating the impact of numerous other factors on satellite cell biology is currently under way.

4.1. Insulin-like growth factors

The IGF system contains two ligands named insulin-like growth factor (IGF)-I and -II [49,50]. Both growth factors play important roles in the regulation of satellite cell activity (reviewed in [12]) [6,18,19], and unlike most growth factors, IGF-I has the ability to stimulate both satellite cell proliferation and differentiation depending on the developmental stage of the myoblast [51–53]. In contrast to the dual roles of IGF-I, IGF-II is thought to be involved solely with satellite cell differentiation. For example, when satellite cells are induced to differentiate by culturing in the presence of low serum-containing medium, IGF-II expression is activated and secretion of IGF-II increases significantly just prior to myoblast differentiation [54]. In fact, introduction of either IGF-I or IGF-II antisense oligonucleotides to cultured media results in partial reduction of differentiated cells [54,55]. Consistent with these findings, pigs carrying a mutation in the IGF-II gene exhibit a three-fold elevation skeletal muscle IGF-II gene expression, which results in significantly greater skeletal muscle mass than their wild-type counterparts [56]. Activated satellite cells also initiate expression of members of the IGF family (e.g. insulin-like growth factor binding proteins [IGFBPs])

and expression of a muscle-specific isoform of IGF-I, termed mechano-growth factor has also been described as an early event in satellite cell activation [57]. Expression of IGFBP-3 and -5 by bovine satellite cells and their involvement in myogenic cell activity has also been reported [58].

Activation of the IGF-I receptor (a receptor tyrosine kinase) on satellite cells initiates intracellular signaling cascades involving both mitogenic and myogenic responses, and the expression of myogenic regulatory factors is induced [59,60]. The working model of IGF-I action (either IGF-I or -II) involves numerous multi-step signal transduction cascades and has been described in recent reviews. IGF-I acts through both the PI3K/AKT as well as the Ras/Raf intracellular signaling pathways [61]. Interestingly, it has been shown that the PI3K activation is necessary for myoblast differentiation and acts through p70 S6 kinase [62,63]. Similarly, IGF-I dependent proliferation of porcine satellite cells appears to involve the mammalian target of the rapamycin (mTOR) pathway [64]. In contrast the Ras-Raf pathway leads to signaling of extracellular response kinases (ERK), which have been shown to be involved in proliferation [60,65]. There is increasing evidence of an interaction between IGF-I signaling and calcineurin that may act to co-coordinate myogenic differentiation in satellite cells [59,66]. While many of these details remain in question, IGF undoubtedly plays an important role in the regulation of satellite cells and skeletal muscle tissue as a whole.

4.2. Myostatin

Transforming growth factor-β (TGF-β) is a well-established negative regulator of satellite cell proliferation and differentiation in domestic animal species (reviewed in [12]). Recently, a new member, myostatin (also known as growth and differentiation factor 8), of the TGF-β superfamily has been identified as a dramatic regulator of skeletal muscle mass. The absence of functional myostatin, as demonstrated in genetically deficient mice and the naturally occurring mutant Piedmontese and Belgian Blue cattle, leads to a substantial increase in skeletal muscle mass otherwise referred to as a "double muscling" phenotype [45,67,68]. On a cellular basis, hyperplasia-related events (increases in muscle fiber number and DNA content) more so than hypertrophic events contribute to the greater skeletal muscle accretion in myostatin-deficient animals [67]. Numerous studies demonstrate that myostatin exerts its effects, at least in part, through the negative regulation of satellite cell activation, proliferation, and differentiation [69–73].

Similar to other TGF-β family members, myostatin initiates intracellular signaling cascades by binding to a type II serine/threonine kinase receptor, exhibiting a preference for ActRIIB [74]. Interaction with the appropriate type II receptor leads to the recruitment and phosphorylation of the type I receptor, either the ALK4 or ALK5 (TβRI) [74,75]. Following receptor activation, the myostatin signal is transmitted via the phosphorylation and activation of the receptor-regulated Smads (R-Smads), Smad2 and Smad3 [74,76,77]. Upon phosphorylation, the Smad2/3 complex forms a heterotrimer with Smad4, a co-mediator Smad (Co-Smad), followed by the translocation of this complex to the nucleus leading to transcriptional activation of TGF-β specific genes [77]. Termination of the myostatin intracellular signaling cascade occurs through a negative feedback mechanism involving Smad7, an inhibitory Smad (I-Smad). Smad7 interferes with formation of the Smad2/3 and Smad4 complexes via competition for activation by type I receptors [78]. Based on the dramatic influence of myostatin on skeletal muscle mass, it is likely that further characterization of the myostatin system has potential for use in developing therapeutic strategies to enhance muscle growth in meat animals and to combat muscle wasting disorders [79,80].

4.3. Fibroblast growth factor

Since the discovery of the first fibroblast growth factor (FGF) as a mitogen in cultured NIH3T3 fibroblasts [81], at least 23 structurally related signaling molecules (FGF1 through FGF23) have been identified belonging to this expanding growth factor family. Numerous FGFs are found in cultured proliferating and differentiated skeletal muscle cells as well as in skeletal muscle tissue [82–84].

FGFs are key players in regulating a variety of biological activities such as cell growth, survival, differentiation and migration. Most FGFs in skeletal muscle are involved in regulating myogenic cell proliferation and differentiation. For example, exogenously added FGF1, 2, 4, 6, and 9 in rat satellite cell culture display a significant mitogenic effect and stimulate cell proliferation above control level [85]. In turkey embryonic myoblasts and satellite cells, FGF2 is required for cell proliferation to occur *in vitro* [86]. Inhibition of endogenous FGF1 synthesis by expressing antisense FGF1 mRNA in a murine myogenic cell line triggers myogenic differentiation [87]. FGF6 (−/−) mutant mice show a severe muscle regeneration defect with fibrosis and myotube degeneration and reduced expression of muscle-specific regulatory factors MyoD and myogenin [88].

FGF signaling is mediated through a family of four transmembrane tyrosine kinase receptors known as FGFR1, FGFR2, FGFR3, and FGFR4, which share similarity in basic structure with specificity on their extracellular ligand-binding domain. FGFR1 and FGFR4 are the most prominent receptors expressed in rat satellite cells *in vitro*, whereas FGFR2 is expressed at a low level and no FGFR3 is detected [88]. The availability of FGF receptor directly regulates FGF signaling that affects skeletal muscle myogenesis. Stable overexpression of a full-length FGFR1 increases cell proliferation and delays differentiation in a murine skeletal myoblast cell line. In contrast, overexpression of a truncated FGFR1 significantly blocks the functional FGF signaling and results in decreasing cell proliferation and enhanced differentiation [89]. Except for the high-affinity FGF receptors, the existence of heparin sulfate (HS) as low-affinity FGF receptors has been well accepted. It is believed that HS interacts with both FGF and FGF receptor to promote FGF-FGFR dimerization and is required for FGF signaling [90].

FGF-binding leads to tyrosine phosphorylation of FGFR and a downstream cascade. Fedorov et al. reported that the expression of oncogenic RAS in skeletal muscle cells induces proliferation and represses terminal differentiation in the absence of exogenous FGFs [91]. Inhibition of mitogen-activated protein kinase kinase (MAPKK) activity completely blocks the FGF2 signal cascade-induced inhibition of skeletal muscle cell differentiation *in vitro* [92]. A recent study by McFarland and Pesall also demonstrated that turkey satellite cells administered FGF2 have increased phospho-mitogen-activated protein kinase (phospho-MAPK) levels, and the variation of phospho-MAPK contributes to the variation of responsiveness to FGF2 stimuli among satellite cell populations [93]. Taken together, although there are various signaling pathways downstream from the activated FGFR, evidence indicates that the activation of the Ras/MAP kinase signaling pathway seems to play a central role in muscle cell responsiveness to FGF in regulating cell proliferation and differentiation.

4.4. Hepatocyte growth factor

Hepatocyte growth factor (HGF), also known as scatter factor, is synthesized as an inactive pro-HGF and proteolytically cleaved into an active, disulfide-linked α-β heterodimer (approximately 90 kDa). Originally identified in liver as a mitogenic factor that stimulates hepatocyte proliferation, HGF is involved in development, homeostasis, and regeneration of a variety of tissues, including skeletal muscle [94]. Among various growth factors that play a role in different stages of myogenesis, HGF is the only one that is reported to activate quiescent skeletal muscle satellite cells and drive them into a cell cycle earlier *in vitro* as well as *in vivo* [95,96]. However, the mechanism involving the HGF activation effect is poorly understood.

HGF is present in an extracellular matrix of the skeletal muscle in active dimer form [97] and co-localizes with its specific receptor c-met in activated satellite cells shortly after muscle injury [95]. Using a hindlimb suspension model, Tatsumi et al. [97] demonstrated that HGF is released in a nitric oxide (NO)-dependent manner since the liberation process is blocked by nitro-L-arginine methyl ester (L-NAME), an inhibitor of NO synthase. Evidence indicated that NO is involved in the activation of matrix metalloproteinase-2 (MMP2) which in turn mediates HGF release from the matrix [98]. Apart from activating quiescent satellite cells, HGF exhibits a mitogenic affect on chicken and turkey satellite cells by increasing satellite cell DNA synthesis in a dose-dependent manner [99,100]. HGF is also an inhibitor of satellite cell differentiation, by suppressing the activity of basic helix-loop-helix (bHLH)/E-protein complexes, thus inhibiting the transactivation of myogenic regulatory factors such as MyoD and myogenin and subsequent muscle-specific protein expression [100]. Further studies have shown that HGF inhibits cell differentiation by coordinately increasing the expression of Twist, an inhibitor of the bHLH transcription factors, while decreasing cyclin-dependent kinase inhibitor $p27^{kip1}$ level [101]. In addition, HGF is reported to have a dose-response mitogenic effect on skeletal muscle satellite cells [102]. HGF-induced cell migration can be strongly increased with exogenous dermatan sulfate (DS) and completely abolished by removing cell surface chondroitin sulfate/DS glycosaminoglycan chains [103].

Although HGF is reported to act in a paracrine mode in mesenchymal cells, an autocrine loop is also described in C2C12 mouse myoblasts and rat primary satellite cells [104,105]. As c-met is the only known receptor for HGF, the dual effect of HGF in regulating skeletal muscle satellite cell proliferation and differentiation seems to be the result of activation of different signal transduction pathways downstream from this receptor. Binding of intracellular mediator protein Grb2 to the phosphorylated tyrosine residues on activated c-met receptors leads to the activation of the Ras-Raf1-MAPK cascade which is essential for cell proliferation [106,107]. In contrast, the coupling of activated c-met receptor with phosphoinositide 3-kinase (PI3K) decreases cell proliferation and results in the activation of the PI3K/AKT pathway that

plays an important role in muscle cell differentiation [108].

5. Steroid hormones

It has long been known that steroids, both androgens and estrogens, influence skeletal muscle and whole body growth, even during the prenatal period. In fact, testosterone is one of the major steroids found in the blood of fetal mammals (for review: [109]). The elevated *in utero* testosterone level of males is believed to be associated with greater postnatal strength of this sex [110], and it is widely recognized that testosterone administration enhances muscle strength in athletes [111]. Although there appears to be considerable individual variation in response, some studies have shown an increase in strength and muscle cross-sectional area of post-menopausal women receiving estrogen/progestin hormone replacement therapy [112,113]. However, an understanding of the mechanisms whereby steroids exert positive effects on skeletal muscle is only recently becoming clearer.

Morphological and histological observations of laboratory animals, meat animals, and humans have pointed to the myogenic satellite cells as principal players behind the mechanism of action of steroids in muscle. Much of the early work focused on the levator ani muscle, a pelvic floor muscle that is particularly sensitive to androgens. Prenatal testosterone levels are responsible for the observed differences in fiber numbers in the male and female levator ani muscle [114]. Joubert and Tobin injected adult female rats with testosterone and examined the effects on this muscle [115]. The results showed that testosterone greatly increased muscle fiber hypertrophy but had no effect on muscle fiber numbers postnatally. These observations were accompanied by increased satellite cell proliferation during the first through third days following administration and increased satellite cell fusion on days 2 and 3. During puberty of male animals, these same changes occurred [116]. Radiotracer studies demonstrated that only 30% of the satellite cells responded to testosterone treatment under several injection protocols utilized [117]. Denervation of the skeletal muscle results in activation of quiescent satellite cells. In castrated males, the activation of satellite cells in the Levator ani muscle fails to occur, suggesting that testosterone is involved in the mediation of satellite cell activation [118].

Further *in vivo* evidence using elderly men led to a connection between testosterone and the insulin-like growth factor (IGF) system [119]. Elderly men normally demonstrate a decrease in serum testosterone levels accompanied by decreased musculature. Testosterone was administered to elderly men having low testosterone levels to produce serum levels similar to that seen in young men. In addition to increased measured muscular strength, RNA protection assays done with skeletal muscle tissue samples showed elevated IGF-I mRNA and decreased IGF binding protein (BP)-4 levels compared with untreated controls. Testosterone administration to elderly men also increased muscle fiber cross-sectional area and satellite cell numbers and activation state [120]. Administration of testosterone to healthy young men was shown to increase satellite cell and mitochondrial area and decrease the nuclear-to-cytoplasmic ratio [121]. The latter is an indication of greater satellite cell activation.

The infusion of nandrolone, a potent anabolic steroid, caused increased IGF-I mRNA, reduced IGF binding protein-4, and increased IGF BP-3 levels in the diaphragm muscles of rats [122]. Additionally, there was increased cross-sectional area of type II muscle fibers.

Many of the early studies examining estrogen effects on skeletal muscle centered on its action following exercise-induced damage. Bär et al. showed that ovariectomized rats exhibited exercised-induced muscle damage similar to males [123]. However, damage was prevented when estradiol was administered just prior to exercise. Additionally, males administered estradiol also did not exhibit exercise-induced muscle damage. More recent experiments [124] demonstrated that exercised male rats administered estrogen exhibited greater satellite cell numbers in soleus and white vastus muscle samples 72 h following a down hill exercise program compared to controls. Enns and Tiidus, using immunohistochemical analysis, showed that there were greater numbers of total, activated and proliferating satellite cells in estrogen-supplemented animals [125]. These results provide evidence that estrogen may influence post-exercise muscle damage by activating satellite cells. Further research [126] supports an additional role of estrogen in muscle physiology. These investigators demonstrated that estrogen administration to rats undergoing muscle immobilization showed significantly decreased muscle atrophy. It was demonstrated that levels of the calcium-activated protease, calpain, was significantly decreased with estrogen treatment and likely participated in the diminished loss of musculature.

In vitro studies using isolated satellite cells have further expanded our knowledge of the involvement of steroids in skeletal muscle growth and physiology. Androgen receptors were identified in porcine skeletal muscles by Doumit et al. [127]. Testosterone administration increased receptor abundance both in satellite cells and myotubes, decreased differentiation, but had no

effect on proliferation. Histochemical analysis identified the presence of androgen receptors in many cell types within skeletal muscle, but predominant expression was localized within satellite cells [128]. Kalbe et al. identified the presence of estrogen receptor-alpha within the nuclei of porcine satellite cells, and estrogen receptor beta was localized within the cytoplasm only [129].

Thompson et al. examined the effect of trenbolone, a testosterone analog long used as a growth promotant in cattle, on satellite cell activity [130]. The addition of trenbolone to cell culture media failed to augment cell proliferation in cultures administered fibroblast growth factor (FGF) or IGF. However, satellite cells derived from trenbolone-treated rats were more responsive to FGF and IGF versus cells from non-treated control animals. Additionally, serum from trenbolone-treated animals stimulated greater proliferation rates than serum from non-treated controls. It was therefore proposed that trenbolone increased the sensitivity of satellite cells to IGF-I and FGF.

Johnson et al. examined the effect of the cattle implant Revalor®-S, which consists of a combination of trenbolone and estradiol, on bovine satellite cell physiology [13]. This implant increases average daily gain and improves feed efficiency of steers. Implantation of steers elevated serum IGF-I levels, whereas IGF-I levels in non-implanted animals either decreased or remained level. Cultures of satellite cells derived from implanted animals exhibited greater fusion percentages, proliferation rates, and myonuclei numbers compared to cultures isolated from control cattle. These data suggest that steroids may influence muscle growth by activation of the satellite cell population. Later work examined the effects of estradiol and trenbolone independently on satellite cells derived from steers [131]. The IGF-I mRNA content of satellite cells increased in cultures of satellite cells administered either estradiol or trenbolone alone. Estradiol also increased satellite cell mRNA levels for the estradiol receptor-alpha, and trenbolone administration increased the expression of the androgen receptor. In myotube cultures, estradiol increased IGF-I expression 2.5-fold versus control myotube cultures. Using serum-containing media stripped of IGF BP-3, both estradiol and trenbolone increased ^{3}H-thymidine incorporation into DNA. However, a more recent report from these investigators [14] indicated that bovine satellite cells administered IGF BP-3 stripped media containing estradiol or trenbolone did not show increased IGF-I mRNA expression. Utilizing specific inhibitors of estrogen, androgen, and the type I IGF receptor, it was confirmed that IGF-I is, indeed, involved in the mechanism of steroid-induced proliferation of satellite cells even when IGF-I mRNA gene expression is unchanged. Further examination of this phenomenon using a G-protein-coupled receptor (GPR)-30 agonist (G1), an estradiol-BSA conjugate and receptor inhibitors determined that estradiol stimulates IGF-I mRNA expression and satellite proliferation via two different mechanisms [132]. Data obtained in these studies indicate that estradiol stimulates proliferation through the classical estrogen receptor while it stimulates IGF-I mRNA expression through binding to GPR-30 [132]. Considerable knowledge has been gained on the mechanism of action of steroids on satellite cell physiology since the previous review [12]. With the advent of new methodologies and approaches, the role of steroids in muscle growth will become even clearer.

6. Muscle-specific transcription factors (MRF) and expression of Pax proteins

Such extrinsic signals impact satellite cell behavior, in part, by altering myogenic regulatory factors including the muscle-specific transcription factors (MRFs) as well as a set of transcription factors called paired box proteins 3 and 7 (Pax3 and Pax7). The MRFs include myogenic determination factor 1 (MyoD), myogenic factor 5 (Myf5) and myogenin (also named myogenic factor 4), which have all been shown to be necessary for muscle formation and for the presence of myogenic cells in adult skeletal muscle [133]. In contrast to the MRFs, whose expression is restricted to myogenic cells, Pax3 and Pax7 expression can be found in developing tissues, including the neuroectoderm and skeletal muscle progenitor cells [134]. In myogenic lineages, Pax3 and Pax7 lie genetically upstream of Myf5 and MyoD and therefore play a critical role in the well-orchestrated myogenic genetic program [135,136].

During quiescence, satellite cells express the transcription factors Pax7, Pax3, and possibly Myf5. Pax7 has widely been recognized as a transcription factor involved in the expression of survival and anti-apoptotic factors. Studies utilizing Pax7-null mice indicate that the loss of Pax7 compromises satellite cell proliferation, ultimately leading to the loss of satellite cell numbers [137,138]. Moreover, recent data show that overexpression of Pax7 in myogenic Pax7-null cells up-regulates MyoD expression while delaying myogenin expression [139,140]. Taken together, this suggests that Pax7 is vital to satellite cell survival and possesses dual roles of inducing myoblast proliferation while delaying differentiation via MyoD regulation [141]. Pax3, a close relative and paralog of Pax7, is essential for embryonic

muscle development, but the functional role of Pax3 in adult muscle is less well understood. Similar to Pax7, Pax3 has been implicated as a participant in satellite cell progression and is transiently expressed during activation [142]. However, high levels of Pax3 expression are restricted to certain muscle types such as the diaphragm [141,143], and therefore the exact role of Pax3 in adult skeletal muscle maintenance remains largely unknown. Finally, Myf5 is thought to regulate proliferation and homeostasis [139,144,145]. It is expressed at relatively high levels in freshly isolated satellite cells; however there appears to be a small population of satellite cells that remains Myf5 inactive [138,143]. Therefore, it is not known if Myf5 is present in quiescent cells, and the exact role of Myf5 remains in question.

During satellite cell activation, the expression of Pax 7, Pax 3, and Myf 5 is retained, coinciding with the initiation of a myogenic genetic cascade involving the expression of the transcription factor, MyoD. Often thought of as the master myogenic transcription factor during satellite cell activation and proliferation [146], MyoD appears to be required for satellite cell differentiation as well. This notion is supported by studies indicating that satellite cells derived from MyoD null mice are able to transition into the differentiation phase, but the process is delayed both *in vitro* and *in vivo* [147,148].

The expression of Pax3, Pax7, Myf5, and MyoD continues as satellite cells transition from activation and enter an active proliferative phase. However, the commitment of satellite cells to a differentiated state is evident by shifts in the transcriptional profile and is marked by the up-regulation of myogenin expression. The requirement of myogenin expression in order to acquire differentiation was confirmed using myogenin-null transgenic mice, where loss of myogenin led to a decrease in muscle size presumably by preventing skeletal myoblast contribution to postnatal muscle growth [149]. The expression of Pax7 is lost during the commitment of myoblasts to the differentiation phase, facilitated in a myogenin-dependent manner [140].

7. Nutrition and satellite cells

Satellite cells of the normal adult animal are essentially dormant and require an activation signal to enter the cell cycle, and once an active participant of the cell cycle; they are controlled by a variety of hormones, growth factors, and metabolites. While it would not be expected that an oral nutrient would directly stimulate satellite cell activation, there are examples of other orally consumed compounds altering satellite cell proliferative and differentiative activity [150]. Additionally, other cell types are known to respond to nutritional compounds [151]. Therefore, it is reasonable to surmise that satellite cells might be affected by a circulating nutritional component.

Several papers have been published describing experiments that may elucidate compounds that might exert a positive influence on satellite cell proliferation or differentiation [152–155]. The compounds tested were of diverse types, including agents that might directly regulate satellite cells (e.g., DHEA), serve as energy-sparing alternatives (e.g., chromium picolinate), act as metabolic intermediates (e.g., creatine), or facilitate the activity of other regulatory compounds (e.g., ferulic acid) [152,153]. One compound, creatine monohydrate, when given orally, was demonstrated to increase rat satellite cell mitotic activity with an increased functional load to the muscle [155]. *In vitro* experiments using Callipyge sheep satellite cells and the direct application of creatine monohydrate to the cell culture medium demonstrated a small, but significant, increase in differentiation and the formation of myotubes [154]. Several subsequent experiments with over 50 different compounds on Callipyge sheep satellite cells did not yield any nutrient component that directly influenced satellite cell proliferation or differentiation.

One possible explanation for the difference in the response of satellite cells *in vivo* compared to *in vitro* is potential processing of the nutrient by the body. Adding compounds directly to the cell culture assumes that the compound can bind to a receptor, be seen by the satellite cell as active, or cross the plasma membrane and act intracellularly. Nutrients taken orally are taken in by enterocytes and altered or allowed into circulation where other cells (such as hepatocytes) may metabolize the compound into a useful metabolite—one that may alter satellite cell activity.

8. Satellite cells and other cell phenotypes

Satellite cells in adult mouse skeletal muscle are multipotential stem cells that can display osteoblast, adipocyte and myotube differentiation [156,157]. Furthermore, myoblasts are able to convert into other mesenchymal lineages including adipocytes and osteoblasts [158,159]. Conversion or differentiation of one phenotype to the other can represent transdifferentiation, which is an irreversible switch of a differentiated satellite cell or myoblast to another type of differentiated cell [160,161]. It is important to note that the conversion process can be indirect if the satellite cell or myoblast does not express key markers of differentiation and therefore is not truly

differentiated at the time of the conversion [156,157]. Discoveries in mouse satellite and myogenic cell studies have generated research on satellite and myogenic cell developmental potentials in domestic animals. Recent *in vitro* studies indicate that satellite cells from several species, including several domestic species, are multipotent cells that can undergo myogenic, adipogenic, and even osteogenic differentiation [162–165]. In these studies there is no evidence of transdifferentiation of satellite cells, since myogenic markers were apparently not evaluated, and myotubes were absent in satellite cell cultures exposed to adipocyte- or osteocyte-inducing media [162–165]. Regardless, the differentiation of satellite cells to adipocytes was dependent on the addition of thiazolidinediones and was associated with the expression of adipocyte markers and PPARγ and/or C/EBPα expression. These markers were consistently absent from satellite cells in non-adipogenic media even with rosiglitazone treatment [163].

The influence of muscle per se on adipose conversion of rat satellite cells was examined in cells isolated from several muscles including the soleus, tibialis anterior, and quadriceps muscles [165]. The adipogenic potential of satellite cells was positively correlated with type I myofiber distribution in the muscle of origin as judged by lipid and C/EBPα-staining. These results demonstrated that the potential of satellite cells to become adipocyte-like is dependent on the muscle of origin [165]. Possibly, blood flow may potentiate or augment muscle-dependent satellite cell adipogenesis, since capillary number per muscle fiber is also positively correlated with type I myofiber distribution.

Aging was shown to markedly increase the adipogenic potential of myoblasts [158,159]. Myoblasts isolated from mouse skeletal muscle at 8 and 23 months of age demonstrated that only myoblasts from 23-month-old mice differentiated into adipocytes [158,159]. Adipocyte conversion was associated with increased expression of C/EBPα and PPARγ 2 which appeared to be regulated by phosphorylation, being more highly phosphorylated in myoblasts isolated from younger animals [159]. Despite adipogenic gene expression, myogenic gene expression was not repressed in myoblasts from aged animals. Furthermore, aging studies and studies of myoblasts from Wnt10b null mice indicated that the balance between myogenic and adipogenic potential in myoblasts may be controlled by Wnt signaling [158,159]. Possibly, aging and Wnt signaling are also involved in dictating the adipogenic potential of satellite cells.

Several studies demonstrate the pivotal role of PPARγ in adipose differentiation of myogenic cells. For instance, the ability of porcine PPARγ to stimulate transdifferentiation of myoblasts to adipocytes was examined by overexpressing wild-type PPARγ or mutated PPARγ (serine 112 was mutated to alanine) in mouse C2C12 myoblast cells [166]. The expression of several adipogenic marker genes was increased in cells overexpressing mutated porcine PPARγ. Furthermore, both wild-type and mutant porcine PPARγ-expressing myoblasts differentiated into adipocytes after PPARγ ligand treatment. The expression of several myogenic marker genes was suppressed in PPARγ transfected cells suggesting that porcine PPARγ can convert myoblast cells into adipocytes [166]. Similarly, transient transfection of PPARγ and C/EBPα induced adipogenic differentiation of fetal myoblasts in a PPARγ ligand dependent manner [167].

A conventional collagenase-based procedure was modified to culture muscle stromal-vascular (SV) cells from neonatal porcine muscle after the removal of all visible connective tissue from the excised muscle [168,169]. Although not designed to specifically isolate and study satellite/myogenic cells per se, these studies provide insight on the influence of thiazolidinediones on myogenic cell fate in true co-cultures of preadipocytes and myogenic cells. For instance, both myotubes and preadipocytes differentiated in muscle SV cell cultures on laminin substrata following seeding and plating with fetal bovine serum [169]. Myotube number was much higher on laminin substrata compared with several other substrata, whereas adipogenesis/preadipocyte number in muscle SV cell cultures was independent of substrata [169]. Troglitazone treatment increased adipogenesis and PPARγ immunoreactivity but did not influence myogenesis, suggesting that myogenic cells were not recruited or transdifferentiated to adipocytes [170]. For instance, double staining for lipid and a myoblast/myotube surface marker and a preadipocyte surface marker on companion laminin-coated dishes clearly showed that, after troglitazone treatment, lipid and PPARγ staining was restricted to preadipocytes with no staining in myoblasts/myotubes. It should be noted that troglitazone treatment did not increase preadipocyte size in muscle SV cell cultures [170]. Myogenic/satellite cells are probably a significant proportion of the muscle SV cells, since studies of semitendinosus muscle cells indicate that the majority of myogenic cells in muscle from 1-week-old pigs are satellite cells [171]. In that regard, these studies [168,169] show that the local milieu or environment may influence transdifferentiation or adipose conversion of porcine satellite cells.

9. Nerves and satellite cells

It is well known that denervation results in progressive skeletal muscle atrophy, although the direct and indirect mechanisms of neural influence on satellite cell activities have not been well established. During acute denervation of muscle, the percentage of satellite cells increases, indicating a potential phase of rapid proliferation during the first week after injury. However, a prolonged denervation leads to a significant decline in satellite cell numbers to less than one fifth of the normal control [172,173]. Satellite cell depletion in long-term denervation may result from a decreased potential in cell mitotic activity as well as an accelerated rate of apoptosis. Kuschel et al. reported that $PCNA^+$ satellite cells were found on isolated myofibers from normal and 4 days post-denervation adult rat muscle but not on myofibers from denervated muscle for 1 week or longer, implying that long-term denervation may cause satellite cells to lose their capability to enter the mitotic cycle [147]. Another study showed that high levels of MRF4 protein were detected in satellite cell nuclei of muscles denervated for 2–3 days but that no detectable signals were found in injured samples by 14 days or longer [174]. Satellite cells derived from muscle 6 and 10 weeks after nerve transection demonstrated a nearly two-fold increase in the rate of apoptosis compared to control cells from innervated muscle [175]. Evidence of direct neural impacts on satellite cells is limited but appears to involve neurotrophic factors such as nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF) in the regulation of satellite cell activities. Muscle-derived stem cells directly exposed to NGF stimulation exhibit significantly reduced differentiation ability *in vitro* [176]. BDNF and its receptor $p75^{NTR}$ co-localize in satellite cells, and the expression of BDNF is reduced dramatically during myogenic differentiation. The repression of BNDF and $p75^{NTR}$ expression in cultured satellite cells significantly enhances cell differentiation [177]. Taken together, these data support roles for neural regulation of satellite cell behavior, which may involve both direct and indirect mechanisms of action. However, information is non-existent in agriculturally important species.

10. Implications

The extrinsic regulation of satellite cells remains an area of research that produces potentially useful knowledge for a variety of disciplines. While experiments have ranged from assessing satellite cell populations for stem cell-like activity to using defined systems to document the cellular or molecular mechanisms of growth regulator action, it is common to find some reference to the extrinsic regulation of the cells in nearly all papers. From a meat animal perspective, two issues are relevant with respect to this line of research. First, an acceptable regimen might be devised to increase the activity of myogenic satellite cells during the rapid growth phase, thereby increasing the efficiency of lean meat production. Second, as satellite cells have been shown to undergo transdifferentiation to form other types of cells, a treatment option might be devised to regulate satellite cell activity during the finishing phase to increase the number of intramuscular adipocytes. Knowledge of the extrinsic regulation of myogenic satellite cells is the first step towards a positive outcome of these two goals.

References

[1] Zammit PS, Partridge TA, Yablonka-Reuveni Z. The skeletal muscle satellite cell: the stem cell that came in from the cold. J Histochem Cytochem 2006;54:1177–91.
[2] Dhawan J, Rando TA. Stem cells in postnatal myogenesis: molecular mechanisms of satellite cell quiescence, activation and replenishment. Trends Cell Biol 2005;15:666–73.
[3] Anderson JE. The satellite cell as a companion in skeletal muscle plasticity: currency, conveyance, clue, connector and colander. J Exp Biol 2006;209:2276–92.
[4] Wozniak AC, Kong J, Bock E, Pilipowicz O, Anderson JE. Signaling satellite-cell activation in skeletal muscle: markers, models, stretch, and potential alternate pathways. Muscle Nerve 2005;31:283–300.
[5] Allen RE, Dodson MV, Boxhorn LK, Davis SL, Hossner KL. Satellite cell proliferation in response to pituitary hormones. J Anim Sci 1986;62:1596–601.
[6] Dodson MV, Allen RE, Hossner KL. Ovine somatomedin, multiplication-stimulating activity, and insulin promote skeletal muscle satellite cell proliferation in vitro. Endocrinology 1985;117:2357–63.
[7] Vierck J, O'Reilly B, Hossner K, Antonio J, Byrne K, Bucci L, et al. Satellite cell regulation following myotrauma caused by resistance exercise. Cell Biol Int 2000;24:263–72.
[8] Le Grand F, Rudnicki MA. Skeletal muscle satellite cells and adult myogenesis. Curr Opin Cell Biol 2007;19:628–33.
[9] Scime A, Rudnicki MA. Anabolic potential and regulation of the skeletal muscle satellite cell populations. Curr Opin Clin Nutr Metab Care 2006;9:214–9.
[10] Holterman CE, Rudnicki MA. Molecular regulation of satellite cell function. Semin Cell Dev Biol 2005;16:575–84.
[11] Zammit P, Beauchamp J. The skeletal muscle satellite cell: stem cell or son of stem cell? Differentiation 2001;68:193–204.
[12] Dodson MV, McFarland DC, Grant AL, Doumit ME, Velleman SG. Extrinsic regulation of domestic animal-derived satellite cells. Domest Anim Endocrinol 1996;13:107–26.
[13] Johnson BJ, Halstead N, White ME, Hathaway MR, DiCostanzo A, Dayton WR. Activation state of muscle satellite cells isolated from steers implanted with a combined trenbolone acetate and estradiol implant. J Anim Sci 1998;76:2779–86.
[14] Kamanga-Sollo E, White ME, Hathaway MR, Chung KY, Johnson BJ, Dayton WR. Roles of IGF-I and the estrogen,

androgen and IGF-I receptors in estradiol-17β- and trenbolone acetate-stimulated proliferation of cultured bovine satellite cells. Domest Anim Endocrinol 2008;35:88–97.
[15] Greenlee AR, Dodson MV, Yablonka-Reuveni Z, Kersten CA, Cloud JG. In vitro differentiation of myoblasts from skeletal muscle of rainbow trout *Oncorhynchus mykiss*. J Fish Biol 1995;46:731–47.
[16] Burton NM, Vierck J, Krabbenhoft L, Bryne K, Dodson MV. Methods for animal satellite cell culture under a variety of conditions. Methods Cell Sci 2000;22:51–61.
[17] Allen RE, Dodson MV, Luiten LS, Boxhorn LK. A serum-free medium that supports the growth of cultured skeletal muscle satellite cells. In Vitro Cell Dev Biol 1985;21:636–40.
[18] Dodson MV, Allen RE. Interaction of multiplication stimulating activity/rat insulin-like growth factor II with skeletal muscle satellite cells during aging. Mech Ageing Dev 1987;39: 121–8.
[19] Dodson MV, Martin EL, Brannon MA, Mathison BA, McFarland DC. Optimization of bovine satellite cell-derived myotube formation in vitro. Tissue Cell 1987;19:159–66.
[20] Iozzo RV. Matrix proteoglycans: from molecular design to cellular function. Annu Rev Biochem 1998;67:609–52.
[21] Bernfield M, Gotte M, Park PW, Reizes O, Fitzgerald ML, Lincecum J, et al. Functions of cell surface heparan sulfate proteoglycans. Annu Rev Biochem 1999;68:729–77.
[22] Yanagishita M. Function of proteoglycans in the extracellular matrix. Acta Pathol Jpn 1993;43:283–93.
[23] Osses N, Brandan E. ECM is required for skeletal muscle differentiation independently of muscle regulatory factor expression. Am J Physiol Cell Physiol 2002;282:C383–94.
[24] Velleman SG, Liu X, Coy CS, McFarland DC. Effects of syndecan-1 and glypican on muscle cell proliferation and differentiation: implications for possible functions during myogenesis. Poult Sci 2004;83:1020–7.
[25] Woods A, Couchman JR. Protein kinase C involvement in focal adhesion formation. J Cell Sci 1992;101(Pt 2):277–90.
[26] Woods A, Couchman JR. Syndecan-4 and focal adhesion function. Curr Opin Cell Biol 2001;13:578–83.
[27] Woods A, Longley RL, Tumova S, Couchman JR. Syndecan-4 binding to the high affinity heparin-binding domain of fibronectin drives focal adhesion formation in fibroblasts. Arch Biochem Biophys 2000;374:66–72.
[28] Zhang L, David G, Esko JD. Repetitive Ser-Gly sequences enhance heparan sulfate assembly in proteoglycans. J Biol Chem 1995;270:27127–35.
[29] Brandan E, Larraín J. Heparan sulfate protoeglycans during terminal skeletal muscle differentiation: Possible functions and regulation of their expression. Basic Appl Myol 1998;8:107–14.
[30] Liu C, McFarland DC, Nestor KE, Velleman SG. Differential expression of membrane-associated heparan sulfate proteoglycans in the skeletal muscle of turkeys with different growth rates. Poult Sci 2006;85:422–8.
[31] Liu X, McFarland DC, Nestor KE, Velleman SG. Developmental regulated expression of syndecan-1 and glypican in pectoralis major muscle in turkeys with different growth rates. Dev Growth Differ 2004;46:37–51.
[32] Brandan E, Carey DJ, Larrain J, Melo F, Campos A. Synthesis and processing of glypican during differentiation of skeletal muscle cells. Eur J Cell Biol 1996;71:170–6.
[33] Iozzo RV. The biology of the small leucine-rich proteoglycans. Functional network of interactive proteins. J Biol Chem 1999;274:18843–6.
[34] Schaefer L, Iozzo RV. Biological functions of the small leucine-rich proteoglycans: from genetics to signal transduction. J Biol Chem 2008.
[35] Nishimura T, Futami E, Taneichi A, Mori T, Hattori A. Decorin expression during development of bovine skeletal muscle and its role in morphogenesis of the intramuscular connective tissue. Cells Tissues Organs 2002;171:199–214.
[36] Schonherr E, Hausser H, Beavan L, Kresse H. Decorin-type I collagen interaction. Presence of separate core protein-binding domains. J Biol Chem 1995;270:8877–83.
[37] Danielson KG, Baribault H, Holmes DF, Graham H, Kadler KE, Iozzo RV. Targeted disruption of decorin leads to abnormal collagen fibril morphology and skin fragility. J Cell Biol 1997;136:729–43.
[38] Ruhland C, Schonherr E, Robenek H, Hansen U, Iozzo RV, Bruckner P, et al. The glycosaminoglycan chain of decorin plays an important role in collagen fibril formation at the early stages of fibrillogenesis. Febs J 2007;274:4246–55.
[39] Allen RE, Boxhorn LK. Inhibition of skeletal muscle satellite cell differentiation by transforming growth factor-beta. J Cell Physiol 1987;133:567–72.
[40] Yamaguchi Y, Mann DM, Ruoslahti E. Negative regulation of transforming growth factor-beta by the proteoglycan decorin. Nature 1990;346:281–4.
[41] Caceres S, Cuellar C, Casar JC, Garrido J, Schaefer L, Kresse H, et al. Synthesis of proteoglycans is augmented in dystrophic mdx mouse skeletal muscle. Eur J Cell Biol 2000;79:173–81.
[42] Zanotti S, Negri T, Cappelletti C, Bernasconi P, Canioni E, Di Blasi C, et al. Decorin and biglycan expression is differentially altered in several muscular dystrophies. Brain 2005;128:2546–55.
[43] Riquelme C, Larrain J, Schonherr E, Henriquez JP, Kresse H, Brandan E. Antisense inhibition of decorin expression in myoblasts decreases cell responsiveness to transforming growth factor beta and accelerates skeletal muscle differentiation. J Biol Chem 2001;276:3589–96.
[44] Cabello-Verrugio C, Brandan E. A novel modulatory mechanism of transforming growth factor-beta signaling through decorin and LRP-1. J Biol Chem 2007;282:18842–50.
[45] Kambadur R, Sharma M, Smith TP, Bass JJ. Mutations in myostatin (GDF8) in double-muscled Belgian Blue and Piedmontese cattle. Genome Res 1997;7:910–6.
[46] Miura T, Kishioka Y, Wakamatsu J, Hattori A, Hennebry A, Berry CJ, et al. Decorin binds myostatin and modulates its activity to muscle cells. Biochem Biophys Res Commun 2006;340:675–80.
[47] Li Y, Li J, Zhu J, Sun B, Branca M, Tang Y, et al. Decorin gene transfer promotes muscle cell differentiation and muscle regeneration. Mol Ther 2007;15:1616–22.
[48] Dodson MV, Mathison BA. Comparison of ovine and rat muscle-derived satellite cells: response to insulin. Tissue Cell 1988;20:909–18.
[49] Humbel RE. Insulin-like growth factors I and II. Eur J Biochem 1990;190:445–62.
[50] Daughaday WH, Rotwein P. Insulin-like growth factors I and II. Peptide, messenger ribonucleic acid and gene structures, serum, and tissue concentrations. Endocr Rev 1989;10:68–91.
[51] Pesall JE, McFarland DC, McMurtry JP, Clapper JA, Francis GL, Gilkerson KK. The effect of insulin-like growth factor analogs on turkey satellite cell and embryonic myoblast proliferation. Poult Sci 2001;80:944–8.

[52] Florini JR, Ewton DZ, Coolican SA. Growth hormone and the insulin-like growth factor system in myogenesis. Endocr Rev 1996;17:481–517.
[53] Engert JC, Berglund EB, Rosenthal N. Proliferation precedes differentiation in IGF-I-stimulated myogenesis. J Cell Biol 1996;135:431–40.
[54] Florini JR, Magri KA, Ewton DZ, James PL, Grindstaff K, Rotwein PS. Spontaneous" differentiation of skeletal myoblasts is dependent upon autocrine secretion of insulin-like growth factor-II. J Biol Chem 1991;266:15917–23.
[55] Ewton DZ, Falen SL, Florini JR. The type II insulin-like growth factor (IGF) receptor has low affinity for IGF-I analogs: pleiotypic actions of IGFs on myoblasts are apparently mediated by the type I receptor. Endocrinology 1987;120:115–23.
[56] Van Laere AS, Nguyen M, Braunschweig M, Nezer C, Collette C, Moreau L, et al. A regulatory mutation in IGF2 causes a major QTL effect on muscle growth in the pig. Nature 2003;425:832–6.
[57] Goldspink G. Mechanical signals, IGF-I gene splicing, and muscle adaptation. Physiology (Bethesda) 2005;20:232–8.
[58] Yi Z, Hathaway MR, Dayton WR, White ME. Effects of growth factors on insulin-like growth factor binding protein (IGFBP) secretion by primary porcine satellite cell cultures. J Anim Sci 2001;79:2820–6.
[59] Musaro A, Rosenthal N. Maturation of the myogenic program is induced by postmitotic expression of insulin-like growth factor I. Mol Cell Biol 1999;19:3115–24.
[60] Coolican SA, Samuel DS, Ewton DZ, McWade FJ, Florini JR. The mitogenic and myogenic actions of insulin-like growth factors utilize distinct signaling pathways. J Biol Chem 1997;272:6653–62.
[61] Moelling K, Schad K, Bosse M, Zimmermann S, Schweneker M. Regulation of Raf-Akt Cross-talk. J Biol Chem 2002;277:31099–106.
[62] Tureckova J, Wilson EM, Cappalonga JL, Rotwein P. Insulin-like growth factor-mediated muscle differentiation: collaboration between phosphatidylinositol 3-kinase-Akt-signaling pathways and myogenin. J Biol Chem 2001;276:39264–70.
[63] Canicio J, Gallardo E, Illa I, Testar X, Palacin M, Zorzano A, et al. p70 S6 kinase activation is not required for insulin-like growth factor-induced differentiation of rat, mouse, or human skeletal muscle cells. Endocrinology 1998;139:5042–9.
[64] Han B, Tong J, Zhu MJ, Ma C, Du M. Insulin-like growth factor-1 (IGF-1) and leucine activate pig myogenic satellite cells through mammalian target of rapamycin (mTOR) pathway. Mol Reprod Dev 2008;75:810–7.
[65] Kamanga-Sollo E, White ME, Hathaway MR, Chung KY, Johnson BJ, Dayton WR. Roles of IGF-I and the estrogen, androgen and IGF-I receptors in estradiol-17beta- and trenbolone acetate-stimulated proliferation of cultured bovine satellite cells. Domest Anim Endocrinol 2008;35:88–97.
[66] Delling U, Tureckova J, Lim HW, De Windt LJ, Rotwein P, Molkentin JD. A calcineurin-NFATc3-dependent pathway regulates skeletal muscle differentiation and slow myosin heavy-chain expression. Mol Cell Biol 2000;20:6600–11.
[67] McPherron AC, Lawler AM, Lee SJ. Regulation of skeletal muscle mass in mice by a new TGF-beta superfamily member. Nature 1997;387:83–90.
[68] Grobet L, Martin LJ, Poncelet D, Pirottin D, Brouwers B, Riquet J, et al. A deletion in the bovine myostatin gene causes the double-muscled phenotype in cattle. Nat Genet 1997;17:71–4.
[69] McFarland DC, Velleman SG, Pesall JE, Liu C. The role of myostatin in chicken (*Gallus domesticus*) myogenic satellite cell proliferation and differentiation. Gen Comp Endocrinol 2007;151:351–7.
[70] McFarland DC, Velleman SG, Pesall JE, Liu C. Effect of myostatin on turkey myogenic satellite cells and embryonic myoblasts. Comp Biochem Physiol A Mol Integr Physiol 2006;144:501–8.
[71] Thomas M, Langley B, Berry C, Sharma M, Kirk S, Bass J, et al. a negative regulator of muscle growth, functions by inhibiting myoblast proliferation. J Biol Chem 2000;275:40235–43.
[72] McCroskery S, Thomas M, Maxwell L, Sharma M, Kambadur R. Myostatin negatively regulates satellite cell activation and self-renewal. J Cell Biol 2003;162:1135–47.
[73] Joulia D, Bernardi H, Garandel V, Rabenoelina F, Vernus B, Cabello G. Mechanisms involved in the inhibition of myoblast proliferation and differentiation by myostatin. Exp Cell Res 2003;286:263–75.
[74] Rebbapragada A, Benchabane H, Wrana JL, Celeste AJ, Attisano L. Myostatin signals through a transforming growth factor beta-like signaling pathway to block adipogenesis. Mol Cell Biol 2003;23:7230–42.
[75] Franzen P, ten Dijke P, Ichijo H, Yamashita H, Schulz P, Heldin CH, et al. Cloning of a TGF beta type I receptor that forms a heteromeric complex with the TGF beta type II receptor. Cell 1993;75:681–92.
[76] Zhu X, Topouzis S, Liang LF, Stotish RL. Myostatin signaling through Smad2, Smad3 and Smad4 is regulated by the inhibitory Smad7 by a negative feedback mechanism. Cytokine 2004;26:262–72.
[77] Nakao A, Imamura T, Souchelnytskyi S, Kawabata M, Ishisaki A, Oeda E, et al. TGF-beta receptor-mediated signalling through Smad2, Smad3 and Smad4. Embo J 1997;16:5353–62.
[78] Nakao A, Afrakhte M, Moren A, Nakayama T, Christian JL, Heuchel R, et al. Identification of Smad7, a TGFbeta-inducible antagonist of TGF-beta signalling. Nature 1997;389:631–5.
[79] Tsuchida K. Activins, myostatin and related TGF-beta family members as novel therapeutic targets for endocrine, metabolic and immune disorders. Curr Drug Targets Immune Endocr Metabol Disord 2004;4:157–66.
[80] Roth SM, Walsh S. Myostatin: a therapeutic target for skeletal muscle wasting. Curr Opin Clin Nutr Metab Care 2004;7:259–63.
[81] Gospodarowicz D. Localisation of a fibroblast growth factor and its effect alone and with hydrocortisone on 3T3 cell growth. Nature 1974;249:123–7.
[82] Allen RE, Dodson MV, Luiten LS. Regulation of skeletal muscle satellite cell proliferation by bovine pituitary fibroblast growth factor. Exp Cell Res 1984;152:154–60.
[83] Grass S, Arnold HH, Braun T. Alterations in somite patterning of Myf-5-deficient mice: a possible role for FGF-4 and FGF-6. Development 1996;122:141–50.
[84] Hannon K, Kudla AJ, McAvoy MJ, Clase KL, Olwin BB. Differentially expressed fibroblast growth factors regulate skeletal muscle development through autocrine and paracrine mechanisms. J Cell Biol 1996;132:1151–9.
[85] Sheehan SM, Allen RE. Skeletal muscle satellite cell proliferation in response to members of the fibroblast growth factor family and hepatocyte growth factor. J Cell Physiol 1999;181:499–506.

[86] McFarland DC, Pesall JE, Gilkerson KK. The influence of growth factors on turkey embryonic myoblasts and satellite cells in vitro. Gen Comp Endocrinol 1993;89:415–24.
[87] Fox JC, Hsu AY, Swain JL. Myogenic differentiation triggered by antisense acidic fibroblast growth factor RNA. Mol Cell Biol 1994;14:4244–50.
[88] Floss T, Arnold HH, Braun T. A role for FGF-6 in skeletal muscle regeneration. Genes Dev 1997;11:2040–51.
[89] Scata KA, Bernard DW, Fox J, Swain JL. FGF receptor availability regulates skeletal myogenesis. Exp Cell Res 1999;250:10–21.
[90] Mohammadi M, Olsen SK, Ibrahimi OA. Structural basis for fibroblast growth factor receptor activation. Cytokine Growth Factor Rev 2005;16:107–37.
[91] Fedorov YV, Rosenthal RS, Olwin BB. Oncogenic Ras-induced proliferation requires autocrine fibroblast growth factor 2 signaling in skeletal muscle cells. J Cell Biol 2001;152:1301–5.
[92] Weyman CM, Wolfman A. Mitogen-activated protein kinase kinase (MEK) activity is required for inhibition of skeletal muscle differentiation by insulin-like growth factor 1 or fibroblast growth factor 2. Endocrinology 1998;139:1794–800.
[93] McFarland DC, Pesall JE. Phospho-MAPK as a marker of myogenic satellite cell responsiveness to growth factors. Comp Biochem Physiol B Biochem Mol Biol 2008;149:463–7.
[94] Jennische E, Ekberg S, Matejka GL. Expression of hepatocyte growth factor in growing and regenerating rat skeletal muscle. Am J Physiol 1993;265:C122–8.
[95] Tatsumi R, Anderson JE, Nevoret CJ, Halevy O, Allen RE. HGF/SF is present in normal adult skeletal muscle and is capable of activating satellite cells. Dev Biol 1998;194:114–28.
[96] Allen RE, Sheehan SM, Taylor RG, Kendall TL, Rice GM. Hepatocyte growth factor activates quiescent skeletal muscle satellite cells in vitro. J Cell Physiol 1995;165:307–12.
[97] Tatsumi R, Allen RE. Active hepatocyte growth factor is present in skeletal muscle extracellular matrix. Muscle Nerve 2004;30:654–8.
[98] Yamada M, Sankoda Y, Tatsumi R, Mizunoya W, Ikeuchi Y, Sunagawa K, et al. Matrix metalloproteinase-2 mediates stretch-induced activation of skeletal muscle satellite cells in a nitric oxide-dependent manner. Int J Biochem Cell Biol 2008;40:2183–91.
[99] Zeng C, Pesall JE, Gilkerson KK, McFarland DC. The effect of hepatocyte growth factor on turkey satellite cell proliferation and differentiation. Poult Sci 2002;81:1191–8.
[100] Gal-Levi R, Leshem Y, Aoki S, Nakamura T, Halevy O. Hepatocyte growth factor plays a dual role in regulating skeletal muscle satellite cell proliferation and differentiation. Biochim Biophys Acta 1998;1402:39–51.
[101] Leshem Y, Spicer DB, Gal-Levi R, Halevy O. Hepatocyte growth factor (HGF) inhibits skeletal muscle cell differentiation: a role for the bHLH protein twist and the cdk inhibitor p27. J Cell Physiol 2000;184:101–9.
[102] Bischoff R. Chemotaxis of skeletal muscle satellite cells. Dev Dyn 1997;208:505–15.
[103] Villena J, Brandan E. Dermatan sulfate exerts an enhanced growth factor response on skeletal muscle satellite cell proliferation and migration. J Cell Physiol 2004;198:169–78.
[104] Sheehan SM, Tatsumi R, Temm-Grove CJ, Allen RE. HGF is an autocrine growth factor for skeletal muscle satellite cells in vitro. Muscle Nerve 2000;23:239–45.
[105] Anastasi S, Giordano S, Sthandier O, Gambarotta G, Maione R, Comoglio P, et al. A natural hepatocyte growth factor/scatter factor autocrine loop in myoblast cells and the effect of the constitutive Met kinase activation on myogenic differentiation. J Cell Biol 1997;137:1057–68.
[106] Leshem Y, Gitelman I, Ponzetto C, Halevy O. Preferential binding of Grb2 or phosphatidylinositol 3-kinase to the met receptor has opposite effects on HGF-induced myoblast proliferation. Exp Cell Res 2002;274:288–98.
[107] Leshem Y, Halevy O. Phosphorylation of pRb is required for HGF-induced muscle cell proliferation and is p27kip1-dependent. J Cell Physiol 2002;191:173–82.
[108] Halevy O, Cantley LC. Differential regulation of the phosphoinositide 3-kinase and MAP kinase pathways by hepatocyte growth factor vs. insulin-like growth factor-I in myogenic cells. Exp Cell Res 2004;297:224–34.
[109] Colenbrander B, de Jong FH, Wensing CJG. Changes in serum testosterone concentrations in the male pig during development. J Reprod Fert 1978;53:377–80.
[110] Fink B, Thanzami V, Seydel H, Manning JT. Digit ratio and hand-grip strength in German and Mizos men: cross-cultural evidence for an organizing effect of prenatal testosterone on strength. Am J Hum Biol 2006;18:776–82.
[111] Kadi F. Cellular and molecular mechanisms responsible for the action of testosterone on human skeletal muscle. A basis for illegal performance enhancement. Brit J Pharmacol 2008: 522–8.
[112] Sipilä S, Taaffe DR, Cheng S, Puolakka J, Toivanen J, Suominen H. Effect of hormone replacement therapy and high-impact physical exercise on skeletal muscle in post-menopausal women: a randomized placebo-controlled study. Biochem Soc Med Res Soc 2001;101:147–57.
[113] Sipilä S, Poutamo J. Muscle performance, sex hormones and training in peri-menopausal and post-menopausal women. Scand J Med Sci Sports 2003;13:19–25.
[114] Tobin C, Joubert Y. Testosterone-induced development of the rat levator ani muscle. Devel Biol 1991;146:131–8.
[115] Joubert Y, Tobin C. Satellite cell proliferation and increase in the number of myonuclei induced by testosterone in the levator ani muscle of the adult female rat. Devel Biol 1989;131:550–7.
[116] Joubert Y, Tobin C, Lebart MC. Testosterone-induced masculinization of the rat levator ani muscle during puberty. Dev Biol 1994;162:104–10.
[117] Joubert Y, Tobin C. Testosterone treatment results in quiescent satellite cells being activated and recruited into cell cycle in rat levator ani muscle. Devel Biol 1995;169:286–94.
[118] Nnodim JO. Testosterone mediates satellite cell activation in denervated rat levator ani muscle. Anat Rec 2001;263:19–24.
[119] Urban RJ, Bodenburg YH, Gilkison C, Foxworth J, Coggan AR, Wolfe RR, et al. Testosterone administration to elderly men increases skeletal muscle strength and protein synthesis. Amer J Physiol Endocrin Metab 1995;269:E820–6.
[120] Sinha-Hikim I, Cornford M, Gaytan H, Lee ML, Bhasin S. Effects of testosterone supplementation on skeletal muscle fiber hypertrophy and satellite cells in community-dwelling older men. J Clin Endocrin Metab 2006;91:3024–33.
[121] Sinha-Hikim I, Roth SM, Lee MI, Bhasin S. Testosterone-induced muscle hypertrophy is associated with an increase in satellite cell number in healthy young men. Amer J Physiol Endocrin Metab 2003;285:E197–205.
[122] Lewis MI, Howvitz GD, Clemmons DR, Fournier M. Role of IGF-I and IGF-binding proteins within diaphragm muscle in modulating the effects of nandrolone. Am J Physiol Endocrin Metab 2002;282:E483–90.

[123] Bär PR, Amelink GJ, Oldenburg B, Blankenstein MA. Prevention of exercise-induced muscle membrane damage by oestradiol. Life Sci 1988;42:2677–81.
[124] Tiidus PM, Deller M, Liu XL. Oestrogen influence on myogenic satellite cells following downhill running in male rats: a preliminary study. Acta Physiol Scand 2005;184:67–72.
[125] Enns DL, Tiidus PM. Estrogen influences satellite cell activation and proliferation following downhill running in rats. J Appl Physiol 2008;104:347–53.
[126] Sugiura T, Ito N, Goto K, Naito H, Yoshioka T, Powers SK. Estrogen administration attenuates immobilization-induced skeletal muscle atrophy in male rats. J Physiol Sci 2006;56:393–9.
[127] Doumit ME, Cook DR, Merkel RA. Testosterone up-regulates androgen receptors and decreases differentiation of porcine myogenic satellite cells in vitro. Endocrinology 1996;137:1385–94.
[128] Sinha-Hikim I, Taylor WE, Gonzalez-Cadavid NF, Zheng W, Bhasin S. Androgen receptors in human skeletal muscle and cultured muscle satellite cells: upregulation by androgen treatment. J Clin Endocrin Metab 2004;89:5245–55.
[129] Kalbe C, Mau M, Wollenhaupt K, Rehfeldt C. Evidence for estrogen receptor α and β expression in skeletal muscle of pigs. Histochem Cell Biol 2007;127:95–107.
[130] Thompson SH, Boxhorn LK, Kong W, Allen RE. Trenbolone alters the responsiveness of skeletal muscle satellite cells to fibroblast growth factor and insulin-like growth factor I. Endocrinol 1989;124:2110–7.
[131] Kamanga-Sollo E, Pampusch MS, Xi G, White ME, Hathaway MR, Dayton WR. IGF-I mRNA levels in bovine satellite cell cultures: effects of fusion and anabolic steroid treatment. J Cell Physiol 2004;201:181–9.
[132] Kamanga-Sollo E, White ME, Chung KY, Johnson BJ, Dayton WR. Potential role of G-protein-coupled receptor 30 (GPR30) in estradiol-17β-stimulated IGF-I mRNA expression in bovine satellite cell cultures. Domest Anim Endocrinol 2008;35:254–62.
[133] Kassar-Duchossoy L, Gayraud-Morel B, Gomes D, Rocancourt D, Buckingham M, Shinin V, et al. Mrf4 determines skeletal muscle identity in Myf5:Myod double-mutant mice. Nature 2004;431:466–71.
[134] Buckingham M, Relaix F. The role of Pax genes in the development of tissues and organs: Pax3 and Pax7 regulate muscle progenitor cell functions. Annu Rev Cell Dev Biol 2007;23:645–73.
[135] Seale P, Sabourin LA, Girgis-Gabardo A, Mansouri A, Gruss P, Rudnicki MA. Pax7 is required for the specification of myogenic satellite cells. Cell 2000;102:777–86.
[136] Relaix F, Rocancourt D, Mansouri A, Buckingham M. A Pax3/Pax7-dependent population of skeletal muscle progenitor cells. Nature 2005;435:948–53.
[137] Oustanina S, Hause G, Braun T. Pax7 directs postnatal renewal and propagation of myogenic satellite cells but not their specification. Embo J 2004;23:3430–9.
[138] Kuang S, Charge SB, Seale P, Huh M, Rudnicki MA. Distinct roles for Pax7 and Pax3 in adult regenerative myogenesis. J Cell Biol 2006;172:103–13.
[139] Zammit PS, Relaix F, Nagata Y, Ruiz AP, Collins CA, Partridge TA, et al. Pax7 and myogenic progression in skeletal muscle satellite cells. J Cell Sci 2006;119:1824–32.
[140] Olguin HC, Yang Z, Tapscott SJ, Olwin BB. Reciprocal inhibition between Pax7 and muscle regulatory factors modulates myogenic cell fate determination. J Cell Biol 2007;177:769–79.
[141] Relaix F, Montarras D, Zaffran S, Gayraud-Morel B, Rocancourt D, Tajbakhsh S, et al. Pax3, Pax7 have distinct and overlapping functions in adult muscle progenitor cells. J Cell Biol 2006;172:91–102.
[142] Conboy IM, Rando TA. The regulation of Notch signaling controls satellite cell activation and cell fate determination in postnatal myogenesis. Dev Cell 2002;3:397–409.
[143] Day K, Shefer G, Richardson JB, Enikolopov G, Yablonka-Reuveni Z. Nestin-GFP reporter expression defines the quiescent state of skeletal muscle satellite cells. Dev Biol 2007;304:246–59.
[144] Ustanina S, Carvajal J, Rigby P, Braun T. The myogenic factor Myf5 supports efficient skeletal muscle regeneration by enabling transient myoblast amplification. Stem Cells 2007;25:2006–16.
[145] Beauchamp JR, Heslop L, Yu DS, Tajbakhsh S, Kelly RG, Wernig A, et al. Expression of CD34 and Myf5 defines the majority of quiescent adult skeletal muscle satellite cells. J Cell Biol 2000;151:1221–34.
[146] Tapscott SJ. The circuitry of a master switch: MyoD and the regulation of skeletal muscle gene transcription. Development 2005;132:2685–95.
[147] Kuschel R, Yablonka-Reuveni Z, Bornemann A. Satellite cells on isolated myofibers from normal and denervated adult rat muscle. J Histochem Cytochem 1999;47:1375–84.
[148] White JD, Scaffidi A, Davies M, McGeachie J, Rudnicki MA, Grounds MD. Myotube formation is delayed but not prevented in MyoD-deficient skeletal muscle: studies in regenerating whole muscle grafts of adult mice. J Histochem Cytochem 2000;48:1531–44.
[149] Knapp JR, Davie JK, Myer A, Meadows E, Olson EN, Klein WH. Loss of myogenin in postnatal life leads to normal skeletal muscle but reduced body size. Development 2006;133:601–10.
[150] Ricks CA, Dalrymple RH, Baker PK, Ingle DL. Use of a β-agonist to alter fat and muscle deposition in steers. J Anim Sci 1984;59:1247–55.
[151] Rayalam S, Della-Fera MA, Baile CA. Phytochemicals and regulation of the adipocyte life cycle. J Nutr Biochem 2008;19:717–26.
[152] Fernyhough ME, Bucci LR, Feliciano J, Vierck JL, Helterline D, Dodson MV. Myogenic satellite cell proliferative and differentiative responses to components of common oral ergogenic supplements. Res Sports Med 2004;12:161–90.
[153] Fernyhough ME, Bucci LR, Feliciano J, Vierck JL, Icenoggle D, Dodson MV. Commonly consumed oral herbal supplements do not influence satellite cell activity. Res Sports Med 2004;12:71–93.
[154] Vierck JL, Icenoggle DL, Bucci L, Dodson MV. The effects of ergogenic compounds on myogenic satellite cells. Med Sci Sports Exerc 2003;35:769–76.
[155] Dangott B, Schultz E, Mozdziak PE. Dietary creatine monohydrate supplementation increases satellite cell mitotic activity during compensatory hypertrophy. Int J Sports Med 2000;21:13–6.
[156] Wada MR, Inagawa-Ogashiwa M, Shimizu S, Yasumoto S, Hashimoto N. Generation of different fates from multipotent muscle stem cells. Development 2002;129:2987–95.
[157] Asakura A, Komaki M, Rudnicki M. Muscle satellite cells are multipotential stem cells that exhibit myogenic, osteogenic, and adipogenic differentiation. Differentiation 2001;68:245–53.

[158] Vertino AM, Taylor-Jones JM, Longo KA, Bearden ED, Lane TF, McGehee REJ, et al. Wnt10b deficiency promotes coexpression of myogenic and adipogenic programs in myoblasts. Mol Biol Cell 2005;16:2039–48.

[159] Taylor-Jones JM, McGehee RE, Rando TA, Lecka-Czernik B, Lipschitz DA, Peterson CA. Activation of an adipogenic program in adult myoblasts with age. Mech Ageing Dev 2002;123:649–61.

[160] Thowfeequ S, Myatt EJ, Tosh D. Transdifferentiation in developmental biology, disease, and in therapy. Dev Dyn 2007;236:3208–17.

[161] Molnar GR, Dodson MV. Satellite cells isolated from sheep skeletal muscle are heterogeneous. Basic Appl Myol 1993;3:173–80.

[162] Singh NK, Chae HS, Hwang IH, Yoo YM, Ahn CN, Lee S, et al. Transdifferentiation of porcine satellite cells to adipoblasts with ciglitizone. J Anim Sci 2007:85.

[163] De Coppi P, Milan G, Scarda A, Boldrin L, Centobene C, Piccoli M, et al. Rosiglitazone modifies the adipogenic potential of human muscle satellite cells. Diabetologia 2006;49:1962–73.

[164] Kook SH, Choi KC, Son YO, Lee KY, Hwang IH, Lee HJ, et al. Satellite cells isolated from adult Hanwoo muscle can proliferate and differentiate into myoblasts and adipose-like cells. Mol Cells 2006;22:239–45.

[165] Yada E, Yamanouchi K, Nishihara M. Adipogenic potential of satellite cells from distinct skeletal muscle origins in the rat. J Vet Med Sci 2006;68:479–86.

[166] Yu YH, Wu SC, Cheng WT, Mersmann HJ, Ding ST. Ectopic expression of porcine peroxisome proliferator-activated receptor delta regulates adipogenesis in mouse myoblasts. J Anim Sci 2008;86:64–72.

[167] Yamanouchi K, Ban A, Shibata S, Hosoyama T, Murakami Y, Nishihara M. Both PPARgamma and C/EBPalpha are sufficient to induce transdifferentiation of goat fetal myoblasts into adipocytes. J Reprod Dev 2007;53:563–72.

[168] Hausman GJ, Poulos S. Recruitment and differentiation of intramuscular preadipocytes in stromal-vascular cell cultures derived from neonatal pig semitendinosus muscles. J Anim Sci 2004;82:429–37.

[169] Hausman GJ, Poulos SP. A method to establish co-cultures of myotubes and preadipocytes from collagenase digested neonatal pig semitendinosus muscles. J Anim Sci 2005;83:1010–6.

[170] Poulos SP, Hausman GJ. A comparison of thiazolidinedione-induced adipogenesis and myogenesis in stromal-vascular cells from subcutaneous adipose tissue or semitendinosus muscle of postnatal pigs. J Anim Sci 2006;84:1076–82.

[171] Mesires NT, Doumit ME. Satellite cell proliferation and differentiation during postnatal growth of porcine skeletal muscle. Am J Physiol Cell Physiol 2002;282:C899–906.

[172] Viguie CA, Lu D-X, Huang S-K, Rengen H, Carlson BM. Quantitative study of the effects of long-term denervation on the extensor digitorum longus muscle of the rat. Anat Rec 1997;248:346–54.

[173] de Castro Rodrigues A, Schmalbruch H. Satellite cells and myonuclei in long-term denervated rat muscles. Anat Rec 1995;243:430–7.

[174] Weis J, Kaussen M, Calvo S, Buonanno A. Denervation induces a rapid nuclear accumulation of MRF4 in mature myofibers. Dev Dyn 2000;218:438–51.

[175] Jejurikar SS, Marcelo CL, Kuzon WM. Skeletal muscle denervation increases satellite cell susceptibility to apoptosis. Plast Reconstr Surg 2002:160–8.

[176] Lavasani M, Lu A, Peng H, Cummins J, Huard J. Nerve growth factor improves the muscle regeneration capacity of muscle stem cells in dystrophic muscle. Hum Gene Ther 2006;17:180–92.

[177] Mousavi K, Jasmin BJ. BDNF is expressed in skeletal muscle satellite cells and inhibits myogenic differentiation. J Neurosci 2006;26:5739–49.